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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/548,883	04/13/2000	Michael I. Watkins	2558B-061300US	7641

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/548,883	WATKINS ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *23-25,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-30* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 15, 2005 has been entered.

Amendment Entry

2. Applicant's amendment and response filed July 15, 2005 is acknowledged and has been entered. The instant specification has also been amended to include a claim for the benefit of priority of a prior filed related application, US application 09/302,920. Claims 23-25, 29 and 30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Currently, claims 1-30 are pending. Claims 1-22 and 26-28 are under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-2, 7-15, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watkins et al. (WO 99/26067) in view of Dietzen (US 5,795,789) and in further view of Weckermann (WO 95/02824).

Watkins et al. disclose a multiplex flow assay for analyzing a single patient sample to simultaneously determine biological markers indicative of thyroid function or disorders (see column 3, lines 6-26). According to Watkins et al., multiple combination assays can be performed on the single patient sample; thus combining competitive, sandwich, immunometric, and serological assays such as assays for thyroid stimulating hormone (TSH) and free thyroxine (T_4) or total T_4 (see column 9, lines 27-34). Specifically, Watkins et al. disclose incubating the sample with a mixture of solid phase particles in a suspension having anti-TSH antibody coated thereto. Simultaneously or

sequentially, the sample is recovered and further incubated with a second anti-TSH antibody that binds another epitope of TSH which is conjugated with a label, i.e. phycoerythrin (see column 8, lines 33-52). Watkins et al. disclose that the solid phase particles may be provided in different groups wherein each group has different antibodies immobilized thereto; i.e. these antibodies in each group are specific to the different immunoglobulin classes such as anti-IgM antibodies and anti-IgG antibodies (see column 10, lines 20-60). Watkins et al. specifically use solid magnetic particles as solid phase which are classifiable by flow cytometry into discrete groups according to distinguishable characteristics, differentiation parameters, and specific antibodies or antigens (assay reagents) which bind in a selective manner (see column 3, lines 6-27 and column 7, line 65 to column 8, line 6). Differentiation parameters include size, fluorescence labels, angle scatter, light emission, density, absorbance, and number of particles for each group (see columns 6-7). The solid particles comprise magnetically responsive materials wherein recovery of these materials after incubation is achieved by subjecting the suspensions to magnetic field to cause the particles to adhere to a reaction vessel wall (see column 3, lines 28-37 and column 8, lines 11-32). Each solid particle group has a fluorescein dye incorporated thereto at differing concentrations and the assay specific antibodies or antigens are labeled with phycoerythrin (see column 6, lines 40-52).

Watkins et al. differ from the instant invention in failing to disclose further assaying the patient sample for triiodothyronine (T_3) and human thyroid peroxidase (hTPO) as biological markers in determining thyroid disorder or function.

Dietzen discloses that a full understanding of thyroid function requires accurate assessment of the amounts of TSH, T_3, and T_4. Dietzen, therefore, provides a standard solution which contains specific amounts of TSH, T_3, and T_4 for use in simultaneous multiple thyroid related-analyte binding assays (see column 2, lines 56-67). The standard also contains serum bovine albumin as the binding protein or diluting agent for the standard (see column 5, lines 15-41). According to Dietzen, large glycoproteins such as TSH are measured by two-site sandwich immunoassay technology, i.e. using anti-TSH antibodies as capture and detection antibodies. Smaller molecules at smaller concentrations such as T_3 and T_4 are determined by competitive hapten immunoassay using anti-T_3 antibodies and anti-T_4 antibodies (see column 6).

Weckermann et al. disclose that human thyroid peroxidase (hTPO) is a glycosylated hemopoietin which is bound to thyroid membranes and performs an important function in the biosynthesis of thyroid hormones (see page 1, paragraph 2). The hTPO is identical to a microsomal antigen which is recognized as autoantigen of circulating anti-thyroid antibodies, i.e. anti-hTPO, (autoantibodies) which are detected in patients having autoimmune disease of the thyroid. These anti-thyroid antibodies, thus, play an important role as biological markers in assessing thyroid function or disorder (see page 2). Weckermann et al. disclose immobilizing monoclonal anti-hTPO antibodies into solid phase particles and labeling anti-hTPO antibodies for use as binding partners in a sandwich assay for quantitative determination of hTPO. The first mAb is specific for a region of the hTPO that is involved in binding of autoantibodies against hTPO. Alternatively, Weckermann et al. disclose preparing standards

comprising hTPO from human thyroid membranes which are purified by affinity chromatography for use in binding assay with anti-hTPO antibodies (see page 11, lines 27-30). Recombinant hTPO is also commercially available in a buffer solution (see page 12, lines 1-8).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Dietzen and Weckerman in assaying for T_3 and hTPO with the multiplex method for assaying TSH and T_4 utilizing groups of identifiable particles, i.e. beads, as taught by Watkins because Watkins specifically taught that his method allows for simultaneous multiple determination and differentiation of physiologically related analytes such as TSH, T_4, T_3, and hTPO which are all analytes that can provide individually and cumulatively, an assessment of thyroid function.

Watkins, Dietzen, and Weckermann have been discussed supra. Watkins, Dietzen, and Weckermann do not teach that hTPO can be coated to particles at a density of 0.3 ng/cm^2 to about 1.0 µg/cm^2 and at a density of 0.5 ng/cm^2 to about 50 ng/cm^2 in claims 18 and 19.

It is, however, maintained that parameters, i.e., density coating of 0.3 ng/cm^2 to about 1.0 µg/cm^2 and 0.5 ng/cm^2 to about 50 ng/cm^2 are all differentiation parameters comprising result effective variables which Watkins has shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the

prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claims 18 and 19 are for any particular purpose or solve any stated problem and the prior art teaches that differentiation parameters often vary according to the reagent being used or sample being assayed, solutions and parameters utilized by Watkins appear to work equally as well. Therefore, absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of the method disclosed by the Watkins by normal optimization procedures.

4. Claims 20-22 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watkins et al. (WO 99/26067) in view of Dietzen (US 5,795,789) and in further view of Weckermann (WO 95/02824) as applied to claims 1-2, 7-15, 18, and 19 above, and further in view of Frengen (US 5,723,346).

Watkins, Dietzen, and Weckermann have been discussed supra. Watkins, Dietzen, and Weckermann differ from the claimed invention in failing to disclose use of two subgroups differing in particle size and/or coating density so as to provide one

subgroup that has greater sensitivity for lower concentrations of TSH and one subgroup that has greater sensitivity for higher concentrations of TSH.

Frengen discloses a binary assay method capable of providing a wide dynamic range and a high degree of precision wherein two subgroups of particles differing from each other in particle size and coating density, i.e. diameter, composition, reactive surface groups, are used (see column 3, lines 47-55 and column 6). Specifically, Frengen discloses reacting a sample with a first binding partner having affinity for a biological marker, i.e. thyroid function marker, a labeled ligand having affinity for the marker, a second binding partner having affinity for the labeled ligand, wherein the first and the second binding partners are independently distinguishable and determinable particle forms and the marker concentrations obtained therefrom are determined using a standard curve (see column 3, lines 56-67).

One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the binary assay using two distinguishable particles taught by Frengen into the multiplex assay method as taught by Watkins because Frengen specifically taught that incorporating binary systems into sandwich assays such as the TSH assay of Watkins provides for a wider or broader dynamic range, particularly in high analyte concentrations wherein the dynamic range would, otherwise, be limited by a phenomenon called hook effect which is usually seen in increased amounts of analyte .

5. Claims 3, 16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watkins et al. (WO 99/26067) in view of Dietzen (US 5,795,789) and in further view of Weckermann (WO 95/02824) as applied to claims 1-2, 7-15, 18, and 19 above, and further in view of Smith et al. (US 4,332,784).

Watkins et al., Dietzen, and Weckermann have been discussed supra. Watkins et al., Dietzen, and Weckermann differ from the instant invention in failing to disclose further assaying the patient sample for anti-thyroglobulins as biological markers in determining thyroid disorder or function.

Smith et al. disclose dual isotope assays for assessing thyroid function or disorder. Smith et al. disclose carrying out an assay for two of TSH, T_3, T_4, and thyroxine binding globulins or thyroglobulin (TBG) which play an important role as biological markers in assessing thyroid function or disorder (see Abstract). Smith et al. disclose an assay for determining T_3 and T_4 using anti-T_4 and anti-T_3 antibodies as immunological binding partners in Example 4, TSH and T_4 using anti-T_4 antibodies and anti-TSH antibodies as immunological binding partners in Example 5, and T_4 and TBG using anti- T_4 and anti-TBG antibodies as immunological binding partners to react and bind T_4 and TBG in Example 6 (see columns 7-8). Smith et al. also use human serum with calibrated T_4 and TBG levels as standards. Smith et al. disclose adding a solution containing 20% w/v polyethylene glycol (PEG) as a solute in the suspension with the binding components to terminate reaction and precipitate bound components in the assay reaction (see column 7, lines 1-6).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Smith in assaying for anti-TBG with the multiplex method for assaying TSH and T_4 utilizing groups of identifiable particles, i.e. beads, as taught by Watkins and modified by Dietzen and Weckerman by additionally assaying for T_3 and hTPO, because Watkins specifically taught that his method allows for simultaneous multiple determination and differentiation of physiologically related analytes such as TSH, T_4, T_3, hTPO, and TBG which are all analytes that can provide individually and cumulatively, an assessment of thyroid function.

Watkins, Dietzen, Weckermann, and Smith have been discussed supra. Watkins, Dietzen, Weckermann, and Smith do not teach concentrations of 0.5% to about 4.0% by weight of PEG in claim 16 and 2.0% to about 3.0% by weight of PEG in claim 17.

It is, however, maintained that parameters, i.e., solute concentrations in assay reagents and buffers, comprise result effective variables which Smith has shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within

the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claims 16 and 17 are for any particular purpose or solve any stated problem and Smith teaches that concentration of PEG often vary according to reagent usage, concentration parameters of PEG utilized by Smith appear to work equally as well. Therefore, absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of the method disclosed by the Smith by normal optimization procedures.

6. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watkins et al. (WO 99/26067) in view of Dietzen (US 5,795,789) and in further view of Weckermann (WO 95/02824) as applied to claims 1-2, 7-15, 18, and 19 above, and further in view Frieden et al. (J. Biol. Chem. (1948), 176, 155-63) and Block et al. (J. Med. Chem. (1976), 19(8), 1067-9).

Watkins et al., Dietzen, and Weckermann have been discussed supra. Watkins et al., Dietzen, and Weckermann differ from the instant invention in failing to disclose an analog composition which is a single species having immunological binding to both anti-triiodothyronine and anti-thyroxine.

Frieden et al. specifically teach that certain thyroxine analogs such as N-acetyl-3,5-diiodo-L-tyrosine previously synthesized by Myers (1932), exhibit physiological thyroxine-like activity and are structurally related as competitive inhibitors for thyroxine.

Block et al. teach synthesizing 3-iodo-L-thyronine and its iodinate derivatives including N-acetyl-3-iodo-L-tyrosine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute thyroxine analogs such as N-acetyl-3,5-diiodo-L-tyrosine as taught by Frieden or N-acetyl-3-iodo-L-tyrosine as taught by Block, for the binding members comprising anti-triiodothyronine and anti-thyroxine in the method of Watkins as modified by Dietzen and Weckermann, because Frieden specifically taught that thyroxine analogs are structurally related as competitive inhibitors for thyroxine and Watkins and Dietzen are generic with the type of immunological binding partners used for T_3 and T_4 in their competitive assays. Further, the N-acetyl-3-iodo-L-tyrosine as synthesized by Block constitutes an obvious modification of thyroxine analogs which are routinely varied in the art and which have not been described as being critical to the practice of the invention.

Response to Arguments

7. Applicant's arguments filed July 15, 2005 have been fully considered but they are not persuasive.

A) Applicant amends the specification to include that the Application claims priority to ASN 09/302,920 filed April 30, 1999, now US Patent 6,280,618, of Michael I. Watkins and Richard B. Edwards. The amendment is for the purpose of claiming priority of US application 09/302,920 as copending application, and relying on the April

30, 1999 filing date to antedate the prior art of record; thus, removing it from the category of prior art, to the extent that it is relevant to the claimed invention.

In response, Applicant fails to meet requirements pre-requite to obtaining a claim of priority status of US application 09/302,920. Applicant's attention is directed to 37 CFR 1.78, wherein it is stated that priority claims must be made within four months of filing of an application. Accordingly, if priority is presented after the four month time period provided which is the case in the instant application, a petition for acceptance of an unintentionally delayed claim for benefit of priority of a prior filed application must be submitted and accompanied by a reference to the prior filed application, indicating relationship thereto, a surcharge set forth in 1.17(t), and a statement that the entire delay was unintentional.

Allowable Subject Matter

8. Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
August 8, 2005